Pulmonary fibrosis: Is inflammation friend or foe?

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Fibrotic interstitial lung diseases (fILDs) present a complex challenge, characterized by progressive fibrosis and often, but not always, significant inflammation. Idiopathic pulmonary fibrosis (IPF), the most common fILD, carries a high mortality rate and is typically marked by limited inflammation, contrasting sharply with other fILDs where inflammation plays a more prominent role. Understanding the dynamic relationship between these processes is essential for optimizing patient care, as therapeutic strategies differ substantially for predominantly fibrotic versus inflammatory ILDs, according to a review in the European Respiratory Journal.1

KEY TAKEAWAYS

- The Pivot: Inflammation and fibrosis are not sequential but dynamically intertwined processes, with their relative importance varying by etiology.
- The Data: Improved understanding of pathomechanisms driving fibrosis is essential for optimizing personalized treatment approaches.
- The Action: Clinicians should consider the specific inflammatory and fibrotic contributions in each fILD phenotype to tailor therapies.

Pulmonary fibrosis, particularly in its idiopathic form, remains a devastating diagnosis with limited therapeutic options. The heterogeneity of fibrotic interstitial lung diseases (fILDs) means that a one-size-fits-all approach to treatment often fails, necessitating a deeper understanding of underlying pathomechanisms.1 These diseases can arise from persistent inflammation triggered by systemic conditions or environmental exposures, but the degree to which inflammation drives or results from fibrosis varies widely across different fILDs.1

Nazemi and colleagues explored the intricate relationship between inflammation and fibrosis in their comprehensive review, highlighting that these are not discrete, sequential events but rather dynamically intertwined processes.1 The authors, including N. Nazemi, B. Crestani, and D.G. Helou, from institutions across Europe, synthesized insights from experimental models and translational research to advance the understanding of these complex interactions.1 Their work emphasizes that the nature and relative importance of these interactions are highly dependent on the underlying etiology of the fILD.1

The Dynamic Relationship of Inflammation and Fibrosis

Inflammation can function as both a driver and a consequence of fibrotic remodeling, establishing self-perpetuating feed-forward loops that exacerbate disease progression.1 But, inflammation also plays a role in fibrosis resolution and control, adding another layer of complexity to its therapeutic targeting.1 This dual nature means that simply suppressing inflammation may not always be beneficial, especially in conditions like IPF where inflammation is often limited, and fibrosis is the dominant feature.1

The review details how fibrotic and inflammatory signaling pathways show considerable overlap, and their interaction is central to disease initiation and progression.1 For instance, various cytokines and growth factors, such as TGF-β, TNF-α, and IL-6, are implicated in both inflammatory responses and profibrotic signaling.1 Understanding these shared pathways offers opportunities for targeted interventions that could modulate both processes simultaneously.1 This is particularly relevant given the broad spectrum of disease phenotypes observed within most fILDs, where the balance between inflammation and fibrosis is only partially determined by the underlying diagnosis.1

Elucidating the mechanisms that govern cellular responses to diverse injurious stimuli provides an opportunity to refine patient stratification and tailor therapies to improve outcomes.1 For example, in fILDs with a significant inflammatory component, anti-inflammatory therapies might be more effective, whereas in predominantly fibrotic diseases, antifibrotic agents would be the primary choice.1 The challenge lies in accurately identifying the dominant pathological process in individual patients, a task that current diagnostic tools do not always accomplish with sufficient precision.1

Current Therapeutic Approaches and Their Limitations

Current therapeutic strategies for fILDs largely bifurcate into anti-inflammatory and antifibrotic approaches.1 For conditions with a clear inflammatory driver, such as connective tissue disease-associated ILDs, immunosuppressive agents like corticosteroids, azathioprine, or mycophenolate mofetil often form the backbone of treatment.1 These agents aim to dampen the immune response and prevent further tissue damage.1 But, their efficacy in purely fibrotic conditions like IPF is limited, and prolonged use carries significant side effects.1

In IPF, the antifibrotic drugs nintedanib and pirfenidone have shown efficacy in slowing disease progression.1 Nintedanib, a tyrosine kinase inhibitor, targets multiple pathways involved in fibrosis, including PDGF, FGF, and VEGF receptors.1 Pirfenidone, an oral antifibrotic agent, reduces fibroblast proliferation and collagen synthesis.1 Both drugs reduce the rate of decline in forced vital capacity (FVC) but do not reverse established fibrosis or cure the disease.1 Their use is associated with side effects such as gastrointestinal disturbances and liver enzyme elevations, which can impact patient adherence.1

The problem is that these antifibrotic agents are not universally effective, and a substantial proportion of patients continue to experience disease progression despite treatment.1 This highlights the unmet need for therapies that can more effectively halt or even reverse fibrosis.1 The limited efficacy of current treatments emphasizes the importance of a personalized approach, where therapies are matched to the specific pathomechanisms driving an individual patient's disease.1 Clinicians seeking a concise guide to modern respiratory practice may find the Oxford Handbook of Respiratory Medicine a useful reference for these complex decisions.

Emerging Targets and Future Directions

Translational research has identified several emerging therapeutic targets that aim to disrupt the feed-forward loops between inflammation and fibrosis.1 These include pathways involved in epithelial cell injury and repair, fibroblast activation, and extracellular matrix remodeling.1 For example, targeting specific inflammatory mediators or their receptors, or inhibiting profibrotic signaling molecules, could offer novel avenues for intervention.1

One area of intense investigation involves the role of specific immune cell subsets in driving fibrosis.1 While IPF is characterized by limited inflammation, other fILDs show variable contributions.1 For instance, certain T-cell subsets and macrophages can either promote or resolve fibrosis depending on their activation state and cytokine profile.1 Modulating

these immune cells, perhaps through novel immunomodulatory agents, could offer a more specific approach than broad immunosuppression.1 This is a concept explored in other fields, such as in chronic graft-versus-host disease, where CAR19 Tregs have shown the ability to suppress immune responses without measurable B cell cytolysis in murine models.3 While not directly applicable to pulmonary fibrosis, this work illustrates the potential for highly specific immune modulation.3

The development of biomarkers that can accurately distinguish between inflammatory and fibrotic phenotypes is also critical.1 Such biomarkers would allow for earlier and more precise patient stratification, guiding treatment decisions towards the most appropriate therapy.1 Imaging techniques, such as advanced CT scans and PET scans, are also being explored for their ability to quantify inflammatory and fibrotic burden in the lungs.1

Another direction involves therapies that directly target the fibrotic process by promoting the degradation of extracellular matrix or inhibiting fibroblast activation.1 This could include agents that modulate lysyl oxidase activity, an enzyme involved in collagen cross-linking, or those that interfere with the activation of myofibroblasts, the primary collagen-producing cells in fibrotic tissue.1 The challenge remains to develop agents that are highly specific to fibrotic pathways without causing undue systemic toxicity.1

The concept of reversing fibrosis, rather than merely slowing its progression, represents the ultimate goal.1 While this remains largely aspirational, experimental models have provided some evidence that fibrosis can be, at least partially, reversible under certain conditions.1 This suggests that therapies aimed at reactivating endogenous antifibrotic mechanisms or promoting tissue regeneration could hold significant potential.1

The Need for Personalized Medicine

The heterogeneity of fILDs demands a personalized medicine approach.1 This means moving beyond a single diagnosis and instead characterizing each patient's disease based on its unique molecular and cellular profile.1 Genetic factors, environmental exposures, and comorbidities all contribute to the diverse phenotypes observed in fILDs.1 For example, patients with systemic sclerosis often develop ILD, and the inflammatory component in these cases may differ significantly from that in IPF.1 Our previous coverage on systemic sclerosis and pulmonary tuberculosis risk highlights the complex relationship of systemic disease and lung pathology.

Integrating multi-omics data (genomics, transcriptomics, proteomics, metabolomics) with clinical and imaging data could provide a more comprehensive picture of each patient's disease.1 This would enable clinicians to select therapies that are most likely to be effective for that individual, minimizing trial-and-error and improving outcomes.1 The insights from experimental models of pulmonary fibrosis and translational research have significantly advanced our understanding of these processes, but translating this knowledge into routine clinical practice remains a substantial hurdle.1

The review by Nazemi, Crestani, and Helou emphasizes that while progress has been made, significant opportunities for improving outcomes in pulmonary fibrosis still exist.1 The focus must shift towards a more granular understanding of the dynamic relationship between inflammation and fibrosis, allowing for the development of tailored therapies.1 This will require continued investment in basic and translational research, as well as the development of robust clinical trials designed to test these personalized approaches.1

The challenge lies in the sheer complexity of these diseases.1 The review acknowledges that while inflammation can drive fibrosis, it can also contribute to its resolution.1 This dual role means that therapeutic interventions must be

carefully calibrated to avoid disrupting beneficial inflammatory processes while targeting detrimental ones.1 The lack of universally accepted biomarkers to precisely differentiate these roles in individual patients remains a significant limitation.1

Still, the emphasis on refining patient stratification and tailoring therapies based on a deeper understanding of pathomechanisms offers a clear path forward.1 This approach moves beyond broad classifications and aims to address the specific drivers of disease in each patient, representing a more sophisticated strategy for managing these challenging conditions.1

CLINICAL IMPLICATIONS

The core message for clinicians managing fibrotic interstitial lung diseases is clear: the days of treating all fILDs as a monolithic entity are over. The evidence from Nazemi and colleagues confirms that inflammation and fibrosis are not simply sequential events but dynamically intertwined processes, with their relative contributions varying significantly by etiology. This demands a more granular diagnostic approach, moving beyond broad labels to identify the dominant pathological drivers in each patient.

For general practitioners and specialists, this means a heightened awareness of the heterogeneity within fILDs. While IPF may present with limited inflammation, other fILDs, particularly those associated with systemic diseases, will have a more pronounced inflammatory component. Tailoring therapy requires a careful assessment of this balance, as anti-inflammatory and antifibrotic agents have distinct mechanisms and efficacy profiles. Prescribing decisions should reflect this specific understanding, rather than a blanket application of antifibrotic drugs.

The industry needs to focus on developing better diagnostic tools and biomarkers that can accurately phenotype fILDs. Without reliable methods to distinguish between predominantly inflammatory versus fibrotic disease, personalized treatment remains an aspiration rather than a reality. Future drug development should also target the specific feed-forward loops identified in the review, aiming for therapies that can modulate both inflammation and fibrosis with greater precision.

For patients, this evolving understanding offers hope for more effective, individualized treatments. It emphasizes the importance of a thorough diagnostic workup and ongoing monitoring to ensure that their therapy aligns with the specific characteristics of their disease. The goal is not just to slow progression but, ideally, to halt or even reverse the fibrotic process, improving long-term outcomes and quality of life.

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